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WORKSHOPS OF THE SOO (2011, LA BAULE). ORIGINAL ARTICLE

Critical study of resection margins in adult soft-tissue sarcoma surgery

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KEYWORDS
Soft-tissue sarcoma;
Resection margins;
Prognostic factors;
Survival;
Local recurrence;
Metastasis

Summary
Introduction: Resection margins constitute a recognized risk factor for local recurrence, but their impact on survival is less clear.
Hypothesis: Infiltrative proliferation and satellite nodules are prognostic factors for local and systemic aggressiveness.
Type of study: Retrospective cohort study.
Patients and methods: In 105 patients under curative treatment, resection quality was assessed on UICC criteria (R0/R1) and on a modified version (R0 M/R1 M) taking account of proliferation contours and satellite nodules for narrow margins (< 1 mm). Uni- and multi-variate analysis was performed, and Kaplan-Meier survival curves were compared on log-rank.
Results: Mean 5-year local recurrence-free survival (LRFS) was 0.64 [0.52—0.76] after R1 surgery, 0.9 [0.85—0.95] after R0, 0.64 [0.519—0.751] after R1 M and 0.92 [0.87—0.96] after R0 M. Resection type according to R classification correlated with disease-free survival (DFS) (P = 0.028), but not with metastasis-free survival (MFS) (P = 0.156). Resection type according to RM classification correlated with DFS and MFS. Multivariate analysis disclosed correlations between LRFS rate and RM resection type (HR 6.77 [1.78—25.7], P = 0.005), DFS rate and RM resection type (HR 2.83 [1.47—5.43], P = 0.001) and grade (HR = 3.17 [1.38—7.27], P = 0.003), and MFS and grade (HR = 3.96 [1.50—10.5], P = 0.006).
Discussion: The microscopic aspect of the proliferation contours and presence of satellite nodules were confirmed as prognostic factors for local and systemic aggressiveness. They impact both disease-free survival and metastasis-free survival in case of margins less than 1 mm. Their systematic consideration may help identify patients with elevated systemic risk.
Level of evidence: IV.

Introduction

Soft-tissue sarcoma (STS) is rarely encountered in everyday practice (incidence, 0.75—1/100,000 per year) [1], and has a

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mortality rate of 50%. Surgery tends to be mutilating. Treatment should follow guidelines and standards to optimize prognosis [1,2]. The current trend is in favor of reference centers [3—5] with appropriate diagnostic and therapeutic methodology and multidisciplinary expertise [6—8].

Treatment is based on adequate surgical resection [9], radiation therapy [5,10] and chemotherapy [11,12], either systemic or by isolated perfusion of the affected limb [13]. Following Simon and Enneking [9,14], limb-conserving surgery has become the gold standard. To achieve resection margins as close to the tumor as possible, assessment of resection quality has become a critical factor in diagnosis and prognosis.

Resection margins [7,9,15—23] represent the main risk factor for local recurrence. Tumor grade [19,20,24,25] and size [15,19,20,24,25] correlate with overall survival. Depth [1,19,20] and histologic type [18,26] have also been considered, but with poor agreement between reports as to their impact on local recurrence, overall survival or both [19,20]. Local recurrence, however, appears as a negative factor in overall survival [25]. Moreover, one-third of high-grade STSs show recurrence despite satisfactory local control [12].

Many prognostic classifications have been published by authoritative bodies: Union for International Cancer Control (UICC), Fédération nationale des centres de lutte contre le cancer (FNCLCC), JOA and SIN (Table 1).

The French FNCLCC consensus system [27,28] is based on the UICC classification [29]: macroscopic residuals (R2), possible microscopic residuals (R1), and *in sano* resection (R0). The data are assessed in the multidisciplinart team meeting, where a treatment program is drawn up; Stoeckle et al. demonstrated the usefulness of this approach [6,7]. The Japanese classification [26] is likewise based on resection margins [14,30], adapted according to histotype, surrounding tissue, chemotherapy and primitive or recurrent tumor status. Engellau recommends a system [12] also taking account of tumor proliferation contours [31], categorized as ''infiltrating'' (poorly defined contours) or ''pushing'' (well defined contours) (Fig. 1).

The present working hypothesis is that, in narrow margins (< 1 mm), proliferation contours and satellite nodules impact local recurrence risk and overall disease-free survival.

A single-center retrospective study recruited 105 patients who had undergone surgery with curative intent. Resection margins were classified using the FNCLCC system (''R'') and on a modified system (''RM'') taking proliferation contours and satellite nodules into account in case of narrow margins.

Patients and methods

The study initially recruited a consecutive series of 189 patients operated on with curative intent between January 2000 and January 2007. Data were collected retrospectively by an independent investigator. The last follow-up date was January 2010; median FU was 42 months (interquartile range, 24—60 months). There was no loss to follow-up.

Inclusion criteria were referral for soft-tissue sarcoma of the extremities or trunk and treatment with curative intent.

Table 1 Characteristics used in soft-tissue sarcoma prognosis systems.

System	Characteristics										
	Margins, residual disease	Consensual approach	Vascular invasion	Necrosis	Size	Proliferation contours	Depth	Response to neoadjuvant treatment	Primitive versus recurrent	Histologic type	Type of surrounding tissue
Enneking	Yes	No	No	No	No	No	No	No	No	No	No
UICC	Yes	No	No	No	No	No	No	No	No	No	No
FNCLCC	Yes	Yes	No	No	No	No	No	No	No	No	No
SIN	No	No	Yes	Yes	Yes	No	No	No	No	No	No
Engellau	No	No	Yes	Yes	Yes	Yes	No	No	No	No	No
AJCC	No	No	No	Yes	Yes	No	Yes	No	No	No	No
JOA	Yes	No	No	No	No	No	No	Yes	Yes	Yes	Yes

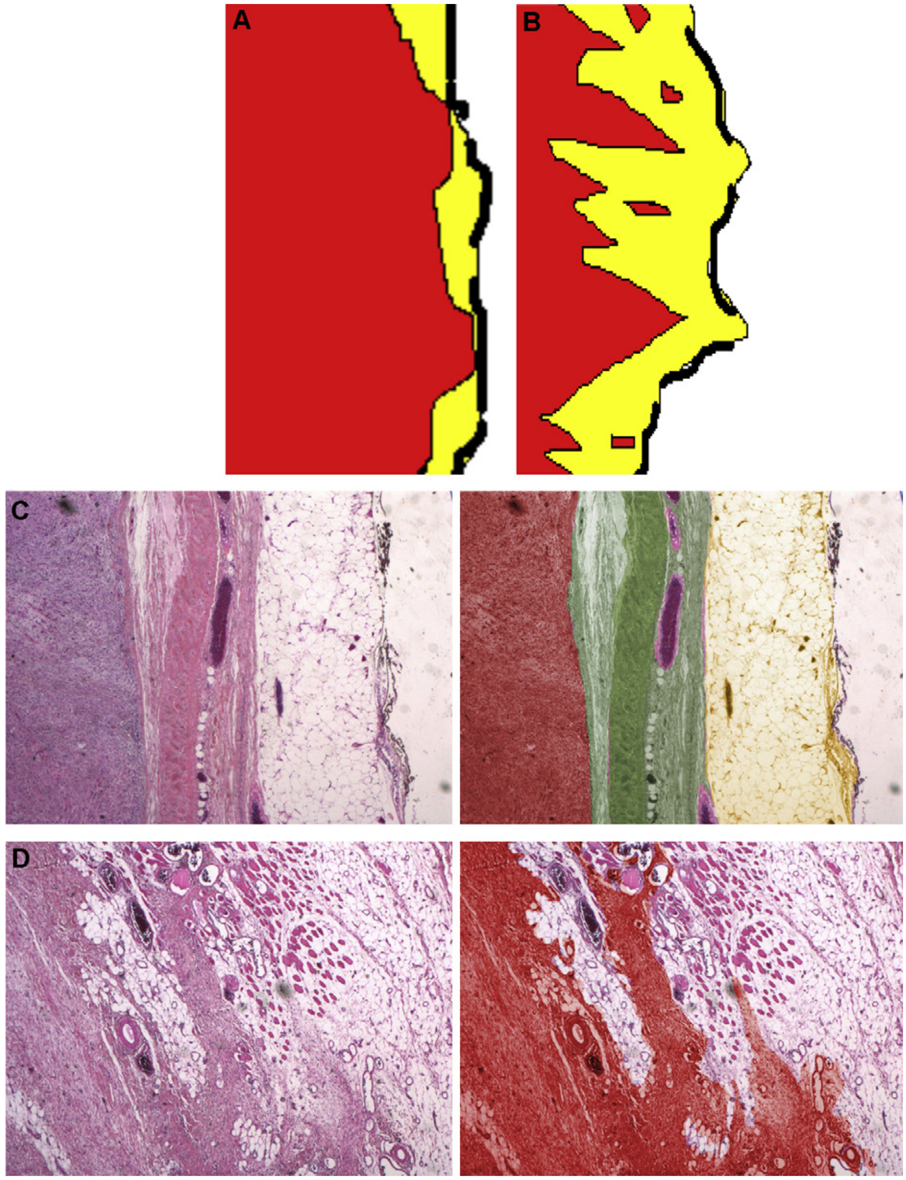

Figure 1 A. Well-contoured proliferation. B. Poorly-contoured proliferation. C. Well-contoured proliferation: aponeurotic plane, fibrous pseudocapsule and adipose tissue plane: grade III malignant histiocytofibroma-like pleomorphic sarcoma. D. Very poorly contoured infiltrative, invasive proliferation: grade I myxofibrosarcoma.

Eighty-four patients were excluded on the flowing criteria:

- low-grade ''lipoma-like'' liposarcoma (47 patients);
- non-respect of the French Sarcoma Group (Groupe sarcome français) Standards, Options and Recommendations [32,33] (24 patients);
- palliative surgery (scheduled R2) (13 patients).

The study series thus comprised 105 patients. Median age was 59 years (14—88); 58 male, 47 female (sex-ratio 1.2:1). Mean tumor size was 8 cm (1—25 cm). In 84 cases (80%), lesions were located in the lower limbs or pelvic belt, 65 in the thigh or buttocks, and 19 in the leg or foot. Twenty (19%) were in the upper limbs or scapular belt, 13 in the arms or shoulders, and 7 in the forearms or hands. In one case, the location was in the trunk. Tumors were primitive in 84 cases (80%) and recurrent in 21 (20%). Twenty-six (25%) were superficial or supra-aponeurotic, and 79 (75%) deep or sub-aponeurotic (Table 2).).

In line with the literature [34], malignant fibrous histiocytoma, undifferentiated sarcoma and pleomorphic sarcoma were grouped together, and represented the most frequent histologic type (50 cases: 48%), followed by leiomyosarcoma (12 cases, 11%) and synovial sarcoma (ten cases, 10%). Histologic grading was on the FNCLCC classification [27,28]: 59 tumors (56%) were grade III, 29 (28%) grade II and eight (8%) grade I.

The following microscopic characteristics were studied: thickness of the thinnest margin (distance between the outermost tumor cells and the resection line, inked with India ink), classification of tumor proliferation contours according

Table 2 Characteristics of study population.

Demographics of patients and tumors		
Characteristics	N	%
Total	105	100
Age, years		
Median	59	56
Interquartile range	47–71	
Gender		
Female	47	45
Male	58	55
Location		
Upper limb	20	19
Trunk	1	1
Lower limb	84	80
Size, cm		
Median	8	
Interquartile range	5–12	
Depth		
Superficial	26	25
Deep	79	75
Presentation		
Primitive	84	80
Recurrent	21	20
Neoadjuvant treatment		
Radiation therapy	5	5
Chemotherapy	16	15
Histologic type		
HFM	50	48
Leiomyosarcoma	12	11
Synovial sarcoma	10	10
Myxoid +Round-cell Liposarcoma	9	9
Rhabdomyosarcoma	5	5
Other	19	18
FNCLCC grade		
I	8	8
II	29	28
III	59	56
Missing data	9	9

Margin characteristics		
Characteristics	N	%
Total	105	100
Contours		
Poorly contoured	36	34
Well contoured	59	56
Missing data	10	10
Margins		
Intra-lesional	21	20
<1 mm	51	49
1–2 mm	17	16
>2 mm	13	12
Missing data	3	3
Satellite nodules		
Present	24	23
Absent or not seen	81	77
Residual disease R (FNCLCC)		
R0	75	71
R1	30	29
Residual disease RM (Modified FNCLCC)		
R0 M	65	62
R1 M	40	38
Type of exeresis		
Compartmental	43	41
Extra-compartmental	62	59
Macroscopic resection		
Wide	56	53
Marginal	46	44
Missing data	3	3
Peroperative capsule rupture		
Contaminated	5	5
Non-contaminated	100	95

to Mandard et al. [31] and presence of satellite nodules. Margins were intra-lesional in 20 cases (19%), less than 1 mm in 51 (49%) and greater than 1 mm in 30 (28%). Proliferation was poorly contoured in 36 cases (34%) and well-contoured in 59 (56%). Non-available data were censured. Resection quality was assessed following the Union for International Cancer Control (UICC) [29], as recommended by the FNCLCC [6]: 30 resections were graded R1 (29%) and 75 (71%) R0.

Margins were re-classified on the ''Modified R'' system (Table 3): resection in greater or equal to 1 mm healthy margin was still graded R0 M, whatever the type of proliferation; margins less than 1 mm or in contact with the tumor were graded R0 M in case of well-contoured proliferation

Table 3 Principles of the ''Modified R'' (RM) classification for residual disease risk.

Minimum thinnest margin thickness	Proliferation contours and satellite nodules	RM Status
≥ 1 mm		ROM
< 1 mm or in contact	Nodules absent, well-contoured	R0 M
< 1 mm or in contact	Poorly contoured and/or nodules present	R1 M

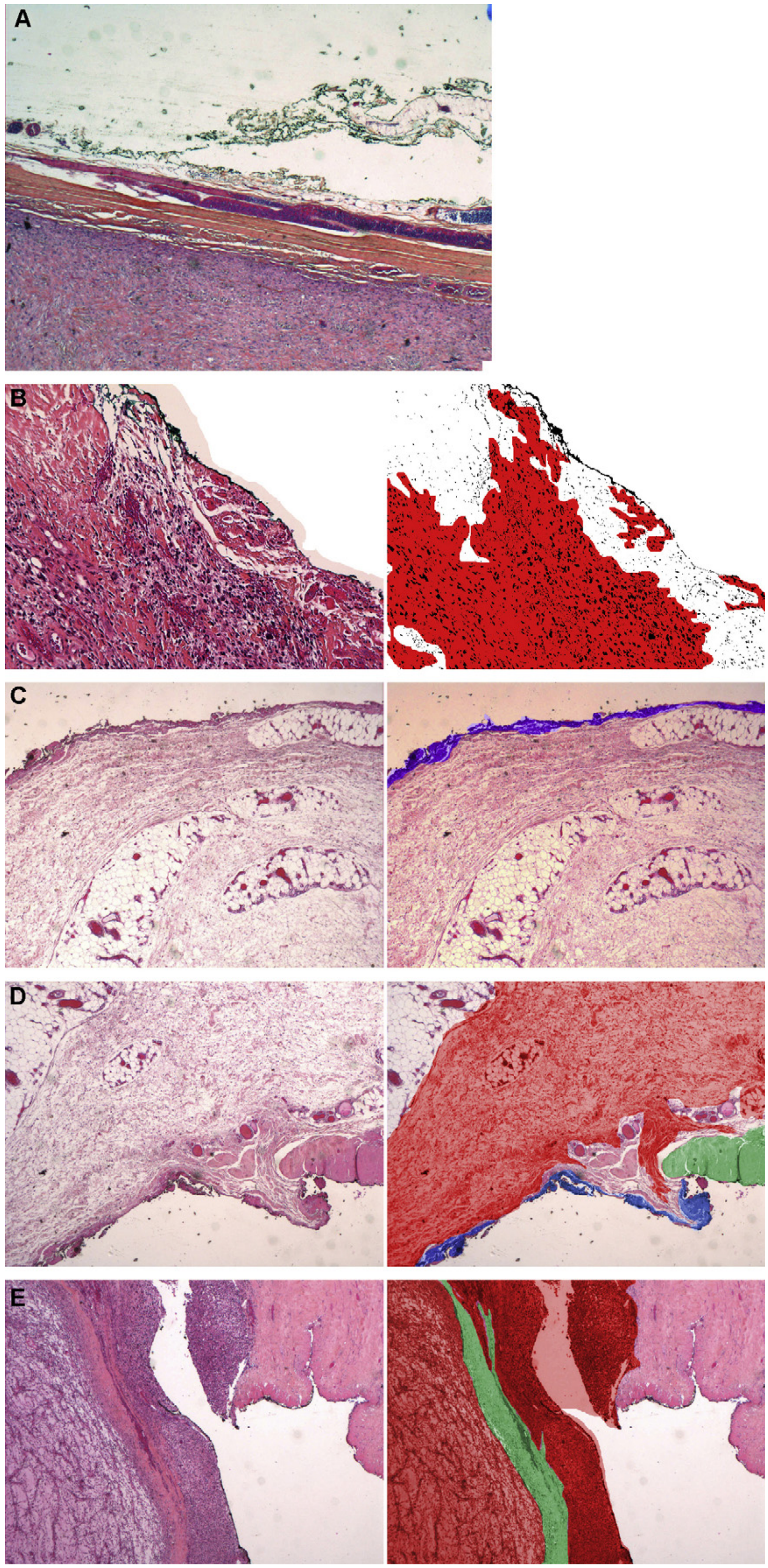

Figure 2 Classification of tumor proliferation contours. A. Margin less than 1 mm, well-contoured proliferation: R0M (grade II myxofibrosarcoma). B. Margin less than 1 mm, poorly-contoured proliferation: R1M (grade III myxoid pleomorphic sarcoma).

and absence of satellite nodules, and R1 M in case of poorly contoured proliferation and/or presence of satellite nodules (Fig. 2).

Macroscopic resection was classified as marginal (46 cases, 44%) or wide (56 cases, 53%), following Enneking [14,30]. In five cases, tumor capsule rupture was found peroperatively, and surgery was classified as contaminated; a standardized procedure was then implemented [35]: the rupture was sutured, the instruments were withdrawn, the affected region was irrigated and suspect areas were resected.

The entire specimen was inked with India ink before formaldehyde fixation.

Adjuvant radiation therapy was used in high-grade tumors with insufficient resection margins. Neoadjuvant anthracycline-based chemotherapy was applied in 16 high-grade tumors, based on histology: synovial sarcoma, rhabdomyosarcoma, soft-tissue osteosarcoma, Ewing sarcoma, angiosarcoma or undifferentiated sarcoma. There were, however, no prospective decision criteria laid down: the decision was made according to individual risk, in the multidisciplinary team meeting.

Statistical analysis used SPSS® software for Windows® (SPSS version 17.0, SPSS Inc., Chicago, IL, USA).

The assessment criteria were: local recurrence-free survival (LRFS), metastasis-free survival (MFS) and disease-free survival (DFS). Time to event occurrence was measured from date of surgery to date of event diagnosis (or last follow-up in case of censure).

Risk factors were explored on univariate analysis. Dichotic variables were compared on log-rank test, and continuous variables on the Cox model.

Multivariate analysis was applied to the most informative variables ($P < 0.2$). Adjusted hazard ratios and 95% confidence intervals were derived from the estimated coefficients. *P*-values < 5% were considered statistically significant.

Survival was analyzed on Kaplan-Meier curves. Distributions were compared on log-rank test.

Results

In the series as a whole, LRFS was 0.87 [0.83—0.91) at 5 years and 0.80 [0.73—0.87] at 10 years; DFS was 0.78 [0.73—0.83] at 5 years and 0.59 [0.45—0.73] at 10 years; MFS was 0.90 [0.86—0.94] at 5 years and 0.76 [0.66—0.86] at 10 years.

Local recurrence-free survival (LRFS)

Local recurrence was diagnosed in 21 of the 105 patients (20%). On univariate analysis (Table 4), infiltrative or poorly contoured proliferation (HR 4.37, [1.27—15.01], $P = 0.02$), peroperative contamination (HR 0.03, [0.00—0.32], $P < 0.004$), R1 surgery (HR 3.61, [1.1—11.86], $P = 0.005$) and R1 M surgery (HR 6.89, [1.82—26.13], $P = 0.035$) were significantly associated with risk of local recurrence (Figs. 3 and 4). On multivariate analysis (Table 5), only R1 M surgery was significantly associated with risk of local recurrence (adjusted HR = 6.77, [1.78—25.7], $P = 0.005$).

On log-rank test, estimated 5-year LRFS was 0.64 [0.52—0.76] following R1 surgery, versus 0.90 [0.85—0.94] after R0 ($P = 0.023$). The RM classification was more discriminative and showed greater significance: estimated 5-year LRFS 0.63 [0.52—0.75] after R1 M surgery and 0.92 [0.87—0.96] after R0 M ($P = 0.001$). Other variables significantly associated with local recurrence risk were tumor grade ($P = 0.03$) and poorly contoured tumor ($P = 0.01$).

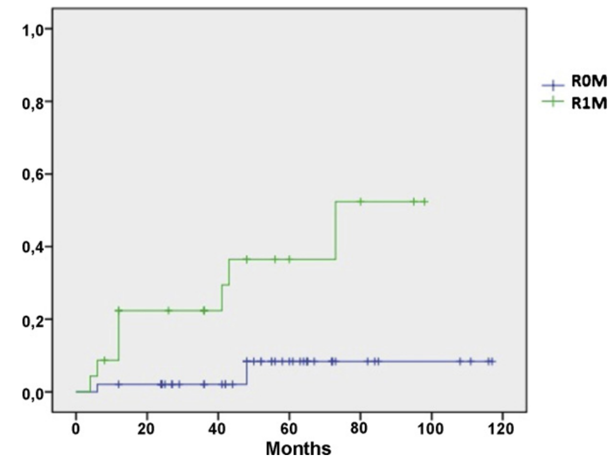

Figure 3 Estimated raw cumulative incidence of local recurrence (LR) on Kaplan-Meier method on the RM (modified FNCLCC) classification (log-rank: $P < 0.001$).

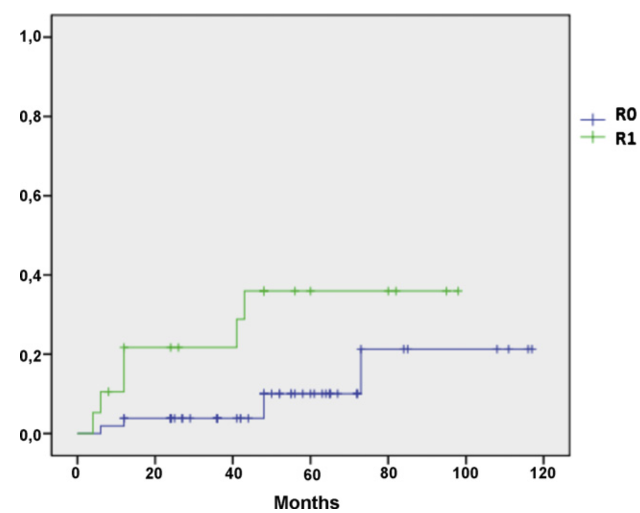

Figure 4 Estimated raw cumulative incidence of local recurrence (LR) on Kaplan-Meier method on the RM (modified FNCLCC) classification (log-rank: $P < 0.03$).

C. Margin less than 1 mm, well contoured: ROM (grade 1 myxofibrosarcoma). D. Margin less than 1 mm, poorly contoured: R1M (grade II myxofibrosarcoma). E. Intralesional resection: R1M (grade III myxoid and pleomorphic sarcoma).

Table 4 Univariate analysis.

Univariate analysis of factors for local recurrence-free survival (LRFS) (*P*-value and 95% confidence interval)

Characteristics (Reference)	Hazard Ratio	95% CI	*P*
Demography			
Gender (male)	1.63	0.48—5.56	0.439
Age (> 60 years)	1.03	0.99—1.06	0.124
Neoadjuvanrt chemotherapy (received)	0.55	0.07—4.32	0.571
Presentation (recurrence)	2.1	0.61—7.22	0.239
Size (> 8 cm)	1.07	0.98—1.18	**0.138**
Tumor			
Location (Thigh)	1.24	0.38—4.06	0.726
Depth(Sub-aponeurotic)	0.98	0.26—3.70	0.975
Grade (3)	4.59	0.99—21.34	**0.052**
Proliferation contours (poorly contoured)	4.37	1.27—15.01	**0.019**
Satellite nodules (present)	3.11	0.90—10.68	**0.072**
Surgery			
Type (extra-compartmental)	0.67	0.20—2.19	0.505
Peroperative contamination (non-contaminated)	0.03	0.00—0.32	**0.004**
Macroscopic resection type (marginal)	3.69	0.97—13.97	**0.055**
Thinnest margin thickness (< 1 mm)	4.96	0.63—39.00	**0.128**
RM (R1 M)	6.89	1.82—26.13	**0.005**
R (R1)	3.61	1.10—11.86	**0.035**

Univariate analysis of factors for disease-free survival (DFS) (*P*-value and 95% confidence interval)

Characteristics (Reference)	Hazard Ratio	95% CI	*P*
Demography			
Gender (male)	1.28	0.69—2.37	0.440
Age (> 60 years)	1.02	1.00—1.04	**0.033**
Neoadjuvanrt chemotherapy (received)	1.25	0.58—2.71	0.569
Presentation (recurrence)	1.27	0.63—2.60	0.504
Size (> 8 cm)	1.04	0.99—1.10	0.140
Tumor			
Location (Thigh)	1.11	0.60—2.04	0.739
Depth (Sub-aponeurotic)	1.14	0.56—2.31	0.727
Grade (3)	3.73	1.64—8.47	**0.002**
Proliferation contours (poorly contoured)	2.56	1.34—4.88	**0.004**
Satellite nodules (present)	2.07	1.10—3.91	**0.024**
Surgery			
Type (extra-compartmental)	1.37	0.72—2.60	0.339
Peroperative contamination (non-contaminated)	2.57	0.99—6.61	**0.051**
Macroscopic resection type (marginal)	1.85	0.97—3.51	**0.061**
Thinnest margin thickness (< 1 mm)	2.09	0.93—4.72	**0.076**
RM (R1 M)	3.05	1.64—5.66	**≤0,001**
R (R1)	1.94	1.05—3.59	**0.033**

Univariate analysis of factors for metastasis-free survival (MFS) (*P*-value and 95% confidence interval)

Characteristics (Reference)	Hazard Ratio	95% CI	*P*
Demography			
Gender (male)	1.21	0.59—2.47	0.607
Age (> 60 years)	1.02	0.99—1.04	0.065
Neoadjuvanrt chemotherapy (received)	1.55	0.67—3.61	0.306
Presentation (recurrence)	1.00	0.41—2.43	0.991
Size (> 8 cm)	1.03	0.97—1.10	0.364

Table 4 (*Continued*).

Characteristics (Reference)	Hazard Ratio	95% CI	*P*
Tumor			
Location (Thigh)	1.11	0.55—2.26	0.766
Depth (Sub-aponeurotic)	1.21	0.52—2.83	0.651
Grade (3)	3.83	1.45—10.12	**0.007**
Proliferation contours (poorly contoured)	2.34	1.09—5.04	**0.028**
Satellite nodules (present)	2.05	0.98—2.48	0.991
Surgery			
Type (extra-compartmental)	1.98	0.88—4.43	**0.097**
Peroperative contamination (non-contaminated)	2.74	0.94—7.97	**0.064**
Macroscopic resection type (marginal)	1.60	0.76—3.35	0.215
Thinnest margin thickness (< 1 mm)	1.73	0.71—4.24	0.228
RM (R1 M)	2.55	1.25—5.20	**0,010**
R (R1)	1.67	0.81—3.45	**0,164**

Data in bold: values of $P < 0.2$ in univariate analysis, used in multivariate analysis. Underlined data: values of $P < 0.05$ or statistically significant in univariate analysis.

Table 5 Significant variables in Cox multivariate models (*P*-value and 95% confidence interval).

Outcome	Risk factor	HR	95% CI	*P*
Local recurrence	R1 M	6.77	1.78—25.7	0.005
Metastasis	Grade 3	3.96	1.5—10.5	0.006
Disease-free survival	R1 M	3.18	1.60—6.32	0.001
	Grade 3	4.27	1.65—11.2	0.003

Disease-free survival (DFS)

At last follow-up, 60 patients (59%) showed no diagnosed local recurrence or metastasis. On univariate analysis, grade-3 tumor (HR = 3.73 [1.64—8.47], $P = 0.002$), poorly contoured proliferation (HR = 2.56 [1.34—4.88], $P = 0.004$), R1 surgery (HR = 1.94 [1.05—3.59], $P = 0.033$), R1 M surgery (HR = 3.05 [1.64—5.66], $P < 0.001$) and satellite nodules (HR = 2.07 [1.10—3.91], $P = 0.024$) were negatively associated with DFS. On multivariate analysis, grade-3 tumor (adjusted HR = 4.27 [1.65—11.2], $P = 0$ .003) and R1 M surgery (adjusted HR = 3.18 [1.60—6.32], $P = 0.001$) were associated.

On log-rank test, estimated 5-year DFS was 0.694 [0.628—0.760] for R0 M surgery and 0.317 [0.228—0.406] for R1 M ($P < 0.001$). On the R classification, estimated 5-year DFS was 0.638 [0.574—0.702] for R0 surgery and 0.356 [0.256—0.456] for R1 ($P = 0.028$). Other variables significantly associated with DFS were poorly contoured margins ($P = 0.003$), grade-3 tumor ($P = 0.001$) and satellite nodules ($P = 0.019$).

Metastasis-free survival (MFS)

At last follow-up, 71 patients (70%) were free of metastasis. On univariate analysis, grade-3 tumor (HR = 3.83 [1.45—10.1], $P = 0.007$), poorly contoured margins (HR = 2.34 [1.09—5.04], $P = 0.028$) and R1 M surgery (HR = 2.55 [1.25—5.20], $P = 0.01$) were significantly associated with occurrence of metastasis and death(Figs. 5 and 6). On multivariate analysis, grade-3 tumor (adjusted HR = 3.96 [1.50—10.5], $P = 0.006$) was associated with MFS.

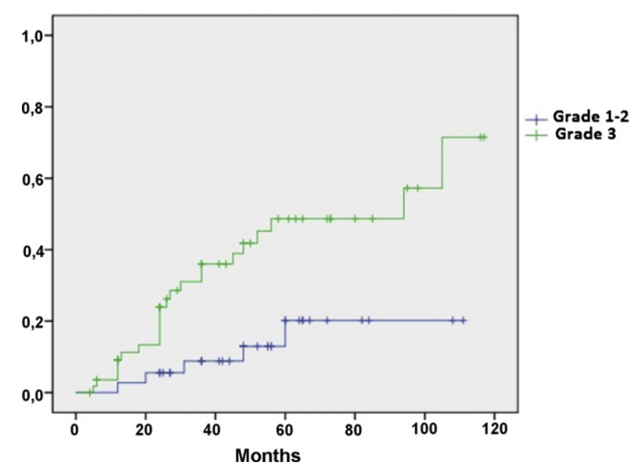

Figure 5 Estimated raw cumulative incidence of metastasis (Kaplan-Meier method) according to Grade (log-rank $P < 0.003$).

On log-rank test, estimated 5-year MFS was 0.751 [0.689—0.813] for R0 M surgery and 0.425 [0.317—0.533] for R1 M ($P = 0.007$). 5-year MFS did not significantly differ ($P = 0.156$) between R0 (0.70 [0.64—0.76] and R1 surgery (0.48 [0.36—0.60]). Other variables significantly associated with MFS were poorly contoured margins ($P = 0.023$), grade-3 tumor ($P = 0.003$) and satellite nodules ($P = 0.05$).

Discussion

The most important finding of the present study is that, in case of narrow (< 1 mm) resection margins, poorly contoured microscopic proliferation and presence of satellite nodules should be taken into account in order to improve the prognostic analysis of residual disease provided by the FNCLCC R system.

This original study in 105 patients sheds new light on how surgery quality in adult soft-tissue sarcoma impacts

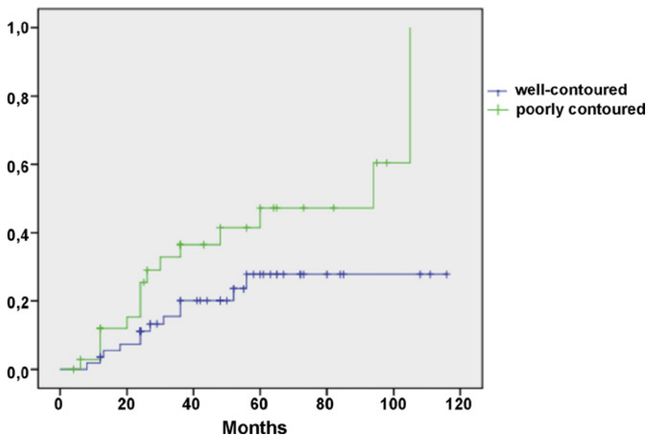

Figure 6 Estimated raw cumulative incidence of metastasis (Kaplan-Meier method) according to contours (log-rank $P = 0.023$).

overall survival as well as local control. The strong points are the single-center design in a sarcoma reference center, with unified management by a specialized team following FNCLCC guidelines, thus avoiding bias inherent to divergent, multicenter management. Moreover, low-grade lipoma-like liposarcomas were excluded, which in other studies introduced bias due to their very different management and evolution, closer to those of locally or locoregionally aggressive lesions [36]: they were identified by Gerrand et al. [18] as a group with low evolutivity in which marginal or intralesional focal resection may be sufficient [37].

The weak points of the study lie in the relatively small series compared to other reports [5,19,20,22,24,38], due to a shorter inclusion period with stricter exclusion criteria. Another limitation was that certain data were missing, so that the corresponding patients were counted as censured in statistical analysis.

The present series was similar to others in terms of general demographic characteristics. The median age was 59 years, compared to 50 for Gronchi et al. [19] and 65 for the Scandinavian Sarcoma Group (SSG) [2]. The initial series included 30% low-grade liposarcoma, compared to 31% for Gronchi et al. [19] and 14% for the SSG [2]. Mean tumor size was 8 cm, compared to 6 cm for Gronchi et al. [19] and 7 cm for the SSG [2]. The rate of inadequate surgery (R1 for scheduled R0 on the UICC system, validated by the FNCLCC) was 29%, comparable to the 26.5% rate in the most recent report (Stoeckle et al. [7]). The 5-year LRFS rate of 90% in adequate surgery (FNCLCC R0) was comparable to that of Stoeckle (93%), who did not exclude low-grade liposarcoma.

Stoeckle's study, published in 2006, was a prospective evaluation of the FNCLCC's consensus prognosis system [2,7,19]. It demonstrated better discrimination for this multidisciplinary resection margin-based approach, with 4-fold elevated risk of type-R1 resection [7]. The method is, however, still based on the UICC system, in which R1 is rather vaguely defined by potential microscopic tumor residue, liable to be interpreted differently from team to team. In our own experience, margins less than 1 mm are harder to interpret. This is borne out by studies [19,39] in which the minimal positive margin was defined by thickness, required to be greater or equal to 1 mm. Sadoski et al. [39] reported little benefit (3%) in local control with margins exceeding 1 mm. The risk of residual disease is harder to assess microscopically, especially where the proliferation area is poorly contoured or where satellite nodules are present. To get around this, we re-classified resection with poorly contoured tumor and/or satellite nodules as ''R1M'', and as ''R0M'' those in which the tumor is well-contoured and there are no satellite nodules.

The present modified UICC system finds support with Mandard et al. [31], who reported unfavorable prognosis for DFS and MFS in case of ''invasive'' resection margins. Engellau [12,40] distinguished ''infiltrative'' and ''pushing'' margins, which he included in a prognostic algorithm which improved the performance of the Scandinavian SIN system. This was founded on his studies [17,40,41] of the Tissue Micro Array (TMA) technique, demonstrating the interest of Ki-67 protein and its independent prognostic value for metastasis.

These findings suggest that tumor proliferation type represents not only a technical problem for surgeons, increasing the risk of intralesional resection and microscopic residue, but also a marker of systemic aggressiveness.

In conclusion, the present proposed modifications in margin classification (RM) could enable more reproductible description of less than 1 mm margins and also, along with other known factors (histological grading, size, subaponeurotic nature), help identify not only patients at risk of local recurrence but also those with poorer survival chances.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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